ErbB4 signaling stimulates pro-inflammatory macrophage apoptosis and limits colonic inflammation.

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Public Summary:
Efficient clearance of pro-inflammatory macrophages from tissues after resolution of a challenge is critical to prevent prolonged inflammation. Defects in clearance can contribute to conditions such as inflammatory bowel disease, and thus may be therapeutically targetable. However, the signaling pathways that induce termination of pro-inflammatory macrophages are incompletely defined. We tested whether the ErbB4 receptor tyrosine kinase, previously not known to have role in macrophage biology, is involved in this process. In vitro, pro-inflammatory activation of cultured murine and human macrophages induced ErbB4 expression; in contrast, other ErbB family members were not induced in pro-inflammatory cells, and other innate immune lineages (dendritic cells, neutrophils) did not express detectable ErbB4 levels. Treatment of activated pro-inflammatory macrophages with the ErbB4 ligand neuregulin-4 (NRG4) induced apoptosis. ErbB4 localized to the mitochondria in these cells. Apoptosis was accompanied by loss of mitochondrial membrane potential, and was dependent upon the proteases that generate the cleaved ErbB4 intracellular domain fragment, suggesting a requirement for this fragment and mitochondrial pathway apoptosis. In vivo, ErbB4 was highly expressed on pro-inflammatory macrophages but not neutrophils during experimental DSS colitis in C57Bl/6 mice. Active inflammation in this model suppressed NRG4 expression, which may allow for macrophage persistence and ongoing inflammation. Consistent with this notion, NRG4 levels rebounded during the recovery phase, and administration of exogenous NRG4 during colitis reduced colonic macrophage numbers and ameliorated inflammation. These data define a novel role for ErbB4 in macrophage apoptosis, and outline a mechanism of feedback inhibition that may promote resolution of colitis.

Scientific Abstract:
Efficient clearance of pro-inflammatory macrophages from tissues after resolution of a challenge is critical to prevent prolonged inflammation. Defects in clearance can contribute to conditions such as inflammatory bowel disease, and thus may be therapeutically targetable. However, the signaling pathways that induce termination of pro-inflammatory macrophages are incompletely defined. We tested whether the ErbB4 receptor tyrosine kinase, previously not known to have role in macrophage biology, is involved in this process. In vitro, pro-inflammatory activation of cultured murine and human macrophages induced ErbB4 expression; in contrast, other ErbB family members were not induced in pro-inflammatory cells, and other innate immune lineages (dendritic cells, neutrophils) did not express detectable ErbB4 levels. Treatment of activated pro-inflammatory macrophages with the ErbB4 ligand neuregulin-4 (NRG4) induced apoptosis. ErbB4 localized to the mitochondria in these cells. Apoptosis was accompanied by loss of mitochondrial membrane potential, and was dependent upon the proteases that generate the cleaved ErbB4 intracellular domain fragment, suggesting a requirement for this fragment and mitochondrial pathway apoptosis. In vivo, ErbB4 was highly expressed on pro-inflammatory macrophages but not neutrophils during experimental DSS colitis in C57Bl/6 mice. Active inflammation in this model suppressed NRG4 expression, which may allow for macrophage persistence and ongoing inflammation. Consistent with this notion, NRG4 levels rebounded during the recovery phase, and administration of exogenous NRG4 during colitis reduced colonic macrophage numbers and ameliorated inflammation. These data define a novel role for ErbB4 in macrophage apoptosis, and outline a mechanism of feedback inhibition that may promote resolution of colitis.